

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07H 17/00	A1	(11) International Publication Number: WO 92/00312 (43) International Publication Date: 9 January 1992 (09.01.92)
(21) International Application Number: PCT/US91/04566 (22) International Filing Date: 26 June 1991 (26.06.91) (30) Priority data: 544,746 27 June 1990 (27.06.90) US (71) Applicant: ASH STEVENS, INC. [US/US]; 5861 John C. Lodge Freeway, Detroit, MI 48202-3398 (US). (72) Inventors: BLUMBERGS, Peter ; 4105 Springer, Royal Oak, MI 48072 (US). KHAN, Mohammed, S. ; Sayyada Mansion, 6-Arazi Bagh, Azamgarh City, U.P.-276001 (IN). KALAMAS, Richard, L. ; 18151 Wilson Court, Wyandotte, MI 48192 (US). PATEL, Ambalal ; 1155 Player Drive, Troy, MI 48089 (US). LAMONTAGNE, Maurice, P. ; 29126 Hemlock Drive, Farmington Hills, MI 48018 (US).		(74) Agent: McLEOD, Ian, C.; 2190 Commons Parkway, Okemos, MI 48864 (US). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent). Published <i>With international search report.</i>
(54) Title: PROCESS FOR THE PREPARATION OF 9-BETA-D-ARABINOFURANOSYL-2-FLUOROADENINE 5'-PHOSPHATE (57) Abstract A process for the preparation of 9-beta-D-arabinofuranosyl-2-fluoroadenine 5'-phosphate (II) from 9-beta-D-arabinofuranosyl-2-fluoroadenine (I) by phosphorylation is described. The reaction is conducted under anhydrous conditions, particularly where (I) is dried extensively in a vacuum. The compound (II) is an antileukemia and antiviral drug.		

Best Available Copy

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TC	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark				

- 1 -

PROCESS FOR THE PREPARATION OF
9-BETA-D-ARABINOFURANOSYL-2-FLUOROADENINE
5'-PHOSPHATE

Cross Reference to Related Application

This application is a continuation-in-part of U.S. Application Serial No. 445,446, filed December 4, 1989.

5 BACKGROUND OF THE INVENTION

(1) Field of the Invention

The present invention relates to an improved process for the preparation of 9-beta-D-arabinofuranosyl-2-fluoroadenine 5'-phosphate (II).
10 In particular, the present invention relates to a process wherein a phosphorylation reaction with 9-beta-D-arabinofuranosyl-2-fluoroadenine (I) is conducted under essentially anhydrous conditions to produce the 5'-phosphate.

15 (2) Prior Art

The preparation and use of 9-beta-D-arabinofuranosyl-2-fluoroadenine, known as 2-F-ara-A (NSC 118218), for the treatment of leukemia and as an antiviral agent is well known and is described in
20 U.S. Patent No. 4,188,378 to Montgomery. The problem is that 2-F-ara-A is very cytotoxic. In an effort to reduce the cytotoxicity 9-beta-D-arabinofuranosyl-2-fluoroadenine 5'-phosphate (NSC 312887; 2-F-ara-AMP) was produced. The conventional phosphorylation reactions produced
25 2-F-araA-AMP in very poor yield and purity. The inability to produce 2-F-araA-AMP in good yields and acceptable purity increased the cost of the drug.

Kim et al J. Carbohydrates Nucleosides-Nucleotides 6(3) 229-236 (1979), Yoshikawa et al. Tet. Letters 50, 5065-5068 (1967), Bull. of the Chem. Soc. Japan 42, 3505-3508 (1969) and Sowa et al., Bull. of
30

-2-

The Chem. Soc. Japan 48, 2084-2090 (1975) describe the formation of 5'-phosphates of various nucleosides. In the first reference it is suggested that the reaction be conducted in conjunction with the addition of a small amount of water to minimize the formation of diesters. Applicant has found this finding to be unnecessary for the preparation of 2-F-ara-AMP. In fact the Applicant has observed that the reaction proceeds best if water is not added to the reaction mixture.

OBJECTS

It is therefore an object of the present invention to provide an improved process for the preparation of 2-F-ara-A-AMP from 2-F-ara-A in good yield and high purity. These and other objects will become increasingly apparent by reference to the following description.

GENERAL DESCRIPTION

The present invention relates to a process for preparing 9-beta-D-arabinofuranosyl-2-fluoroadenine 5'-phosphate (II) which comprises: vacuum drying 9-beta-D-arabinofuranosyl-2-fluoroadenine (I); reacting under essentially anhydrous conditions in a reaction mixture the vacuum dried (I) with a molar excess of an anhydrous tri-lower alkyl phosphate and a phosphorus oxyhalide, wherein the halide is selected from bromine and chlorine, at a reduced temperature to produce an intermediate of (II) in the reaction mixture; adding water to the reaction mixture to hydrolyze the intermediate and to terminate the reaction and provide (II) dissolved in the water; treating the reaction mixture to precipitate (II) from the reaction mixture; and separating the precipitated (II) from the reaction mixture.

It has been found that the 2-F-ara-A must be dried extensively under vacuum and that the reaction must be conducted under essentially anhydrous conditions. The 2-F-ara-A is essentially anhydrous, if not completely anhydrous, as a result of heating under a vacuum to

-3-

eliminate most of the water of hydration. The tri-lower alkyl phosphate is also dried.

The lower alkyl phosphate is preferably trimethyl phosphate. Tri-lower alkyl phosphates where the alkyl groups are 1 to 2 carbon atoms can be used.

After the reaction to form 2-F-ara-AMP (II) is completed, water is added to hydrolyze the intermediate (a 5'-phosphorodichloridate) and to terminate the reaction. The 2-F-ara-AMP (II) dissolves in the water and then is separated from the water. Preferably a non-polar organic solvent which is essentially a non-solvent for 2-F-ara-AMP is used to cause 2-F-ara-AMP (II) to precipitate. The solvent is removed and preferably the 2-F-ara-AMP (II) is dissolved in water and recrystallized from the water. Small amounts of 2-F-ara-AMP (II) are recovered from the solvent.

SPECIFIC DESCRIPTION

9-beta-D-Arabinofuranosyl-2-fluoroadenine 5'-phosphate (II)
NSC 312887

In exploratory work the nucleoside (I), after air-drying, was dried under vacuum at room temperature for several days to yield a monohydrate. The monohydrate dissolved readily (~20 min) in the reaction medium as the reaction proceeded, the excess phosphorus oxychloride appeared adequate to destroy the water of hydration and the yields were unacceptably low. In further work, the nucleoside (I) was dried 24 hours at 0.33 mmHg and 90°C to give essentially anhydrous material. The trimethylphosphate reaction solvent was distilled and the forerun and tail fractions were discarded. With these changes the time to obtain a homogeneous reaction system was extended to 4 to 6 hours and the yields were both reproducible and markedly improved (75-79%, average 76%) based on product (II) as a monohydrate after drying at room temperature for 4 hours at 0.3 mmHg.

A typical 100 g run used to process 785 g of intermediate (I) is described. Phosphorous oxychloride

-4-

(80.0 g, 49 mL, 523 mmol) was added to cold (0°C, ice-bath) anhydrous, redistilled trimethylphosphate (1 L) and the solution was kept at 0°C for 1 hour. Dried 9-beta-D-Arabinofuranosyl-2-fluoroadenine (I) (100.0 g, 350.6 mmol) was added with stirring in one portion. The reaction mixture became homogeneous (light-yellow solution) after 4 to 6 hours. The reaction mixture was then placed in a refrigerator (~1°C) for 15 hours. No starting material was present by tlc. Water (70 mL) was added and the solution was stirred for 3 hours at 0°C. The mixture was then poured into cold (-0°C, ice-bath) methylene chloride (8 L) with stirring and held in the ice-bath with stirring until a clear methylene chloride phase was obtained (1 h). The methylene chloride was removed by decantation and the residual yellowish, gummy mass was dissolved in warm (~50°C) water (700 mL). The solution was seeded and allowed to stand at room temperature overnight. The resulting crystalline product was collected by filtration and washed with water (50 mL) and with ethanol (2 x 50 mL). The product (II) was dried at room temperature at 0.3 mmHg for 4 hours to give 78.5 g (tlc, trace impurities) of first crop material, mp 200-205°C (dec), with prior browning at ~185°C.

The methylene chloride supernatant liquid, which remained after the isolation of the crude gummy product, was extracted with water (3 x 500 mL). The water extracts were combined and percolated into a column containing Dowex-50 (acid form) resin (560 x 80 mm). The column was eluted with water and the fractions containing product (by UV monitor and tlc) were combined. The aqueous solution was then concentrated (aspirator) to a smaller volume (ca. 250 mL) and allowed to cool to ambient temperature overnight. The resulting crystalline solid (II) was removed by filtration, washed with a small portion of water followed by ethanol, and dried as above to give 11.0 g of product (II) with the same purity (by tlc) as that of first crop of (II). In a similar manner the mother liquor from

-5-

the first crop of (II) was treated as described above to give 10.5 g of product of the same purity (tlc) as the other crops. The combined yield was 100 g (70% calculated as the monohydrate).

5 In this manner, 785 g of well-dried (24 h, 90°C, 0.3 mmHg), essentially anhydrous starting nucleoside (I) was processed to give 799 g (76%, calculated as a monohydrate) of good quality target compound (II). However, in the initial series of runs, 510 g of nucleoside
10 as the monohydrate was processed to give but 351 g (54%).

Recrystallization

15 The above material, 1134 g of (II), from five runs was dissolved in preheated deionized water (82°C, 15 mL/g). The compound dissolved in 3-5 minutes at 73-75°C. The solution was filtered through paper and the filtrate
20 was transferred to a 22 L flask. The solution was stirred and cooled rapidly to 45-50°C to minimize product (II) decomposition. At this point, the product (II) started to crystallize and the mixture was allowed to cool slowly overnight to complete the precipitation. If the
25 temperature is allowed to fall to 32-33°C before precipitation is complete, the product will precipitate as a gel which is undesirable. The solution was then cooled (ice-bath) for two hours. The resulting precipitate of (II) was collected by filtration through filter-cloth. The
filter cake of (II) was washed successively with cold deionized water (1.25 L) and ethanol (1.8 L).

30 The product (II) was dried at room temperature at 0.3 mmHg for 24 hours and weighed 916 g as an 0.8 hydrate at this point. The product (II) was dried further at 55-60°C at 0.3 mmHg for 72 hours to give 881 g (82% recovery) of anhydrous material. The average yield of (II) was 67% from the precursor nucleoside (I). The mother liquor can be reworked and additional pure product (II) (ca
35 10%) isolated.

In view of the extensive handling in the last step, a final recrystallization of (II) was necessary to

-6-

remove any inadvertently-introduced water-insoluble impurities. The acidic product is, however, unstable in hot water. Some decomposition occurs during the recrystallization and no real improvement in purity results. With careful handling in the last step, it is possible that the final recrystallization can be avoided.

Materials

trimethylphosphate
Phosphorous oxychloride (d = 1.645)
Methylene chloride
Dowex 50W-X2, 50-100 mesh
Alcohol, 3A, specially denatured

PHYSICAL AND ANALYTICAL DATA2-Fluoro-ara-adenosine 5'-phosphate, NSC 312887

Melting Point: 202-203°C (dec), browns at 190°C.

Analysis: Calcd for $C_{10}H_{13}FN_5O_7P$ (365.21)

		<u>Calcd</u>	<u>Found</u>
20	C	32.89	32.77
	H	3.59	3.74
	N	19.17	19.04
	F	5.20	4.96
	P	8.48	8.40

25 Ultraviolet Spectral Data:

(0.1 N HCl) lambda max (H₂O) 262 nm 13,500

(0.1 N NaOH) lambda max (H₂O) 261 nm 15,600

Thin Layer Chromatograph: (EM Silica gel 60F-254, 240)

30

iso-PrOH-H₂O-NH₄OH (7:2:1), R_f = 0.24, trace impurity

n-PrOH-MeOH-H₂O-NH₄OH (4:3:2:1), R_f = 0.41, trace impurity

MeOH-H₂O-NH₄OH (75:25:1), R_f = 0.70, trace impurity

35

-7-

Solubility Data: 25°C, without heating (Ref 1).

Free Acid:

Water: 9 mg/mL (8.7 and 9.3 mg/mL), 2 det'ns,
pH~2

5 Ethanol: Insoluble

Sodium Salt:

Water: >100 mg/mL (upper limit not determined)

10 It is intended that the foregoing description be
only illustrative of the present invention and that the
present invention be limited only by the hereinafter
appended claims.

15

-8-

I CLAIM:

-1-

A process for preparing
9-beta-D-arabinofuranosyl-2-fluoroadenine 5'-phosphate (II)
in improved yields which comprises:

(a) vacuum drying

5 9-beta-D-arabinofuranosyl-2-fluoroadenine (I);

(b) reacting under essentially anhydrous
conditions in a reaction mixture the vacuum dried (I) with
a molar excess of an anhydrous tri-lower alkyl phosphate
and a phosphorus oxyhalide wherein the halide is selected
10 from bromine and chlorine at a reduced temperature to
produce an intermediate of (II) in the reaction mixture;

(b) adding water to the reaction mixture to
hydrolyze the intermediate and terminate the reaction and
provide (II) dissolved in the water;

15 (c) treating the reaction mixture to
precipitate (II) from the reaction mixture; and

(d) separating the precipitated (II) from the
reaction mixture.

-2-

The process of Claim 1 wherein the tri-lower
alkyl phosphate is trimethyl phosphate.

-3-

The process of Claim 1 wherein phosphorus
oxyhalide is phosphorus oxychloride.

-4-

The process of Claim 1 wherein the tri-lower
alkyl phosphate is trimethyl phosphate and wherein the
phosphorus oxyhalide is phosphorus oxychloride.

-9-

-5-

The process of Claim 1 wherein the temperature is about -2°C to 0°C.

-6-

The process of Claim 5 wherein the reaction in step (a) is conducted for at least about 16 to 18 hours after the reaction mixture becomes homogeneous as a light yellow solution.

-7-

The process of Claim 6 wherein (II) is precipitated from the reaction mixture with methylene chloride as a solvent to precipitate (II) from the reaction mixture.

-8-

The process of Claim 7 wherein (II) is dissolved in water and recrystallized.

-9-

The process of Claim 1 wherein (I) is dried in step (a) is produced by heating to between 85° and 90°C for at least 24 hours in a vacuum of less than about 0.2 mm of Hg.

-10-

The process of Claim 7 wherein the solvent is extracted with water to provide (II) in the water, the water with (II) is eluted through an ionic chromatographic column to provide aqueous fractions containing (II); the aqueous fractions are concentrated using a vacuum and heating to remove some of the water; a mixture of the concentrated aqueous fractions containing (II) is cooled to crystallize (II) from the concentrated solution and (II) is separated from the water.

-10-

-11-

The process of Claim 1 wherein the separated (II) in step (d) is dissolved in heated water and then the heated water is cooled to precipitate (II) which is separated from the water.

-12-

A process for preparing 9-beta-D-arabinofuranosyl-2-fluoroadenine 5'-phosphate (II) in improved yields which comprises:

(a) vacuum drying

5 9-beta-D-arabinofuranosyl-2-fluoroadenine (I);

(b) reacting under essentially anhydrous conditions in a reaction mixture the vacuum dried (I) with a molar excess of anhydrous trimethyl phosphate and a phosphorus oxychloride at a temperature between about -2°C and 0°C to produce an intermediate of (II) in the reaction mixture;

(c) adding water to the reaction mixture to hydrolyze the intermediate and terminate the reaction and provide (II) dissolved in the mixture;

15 (d) treating the reaction mixture with methylene chloride to precipitate (II) from the reaction mixture; and

(e) separating the precipitated (II) from the reaction mixture and the methylene chloride.

20

-13-

The process of Claim 12 wherein the temperature is about 0°C.

-11-

-14-

The process of Claim 13 wherein the reaction is conducted for at least about 16 to 18 hours after the reaction mixture becomes homogeneous as a light yellow solution.

-15-

The process of Claim 12 wherein (II) is dissolved in heated water and recrystallized after step (d).

-16-

The process of Claim 12 wherein (I) is dried (I) in step (a) is produced by heating to between 85° and 90°C for at least 24 hours in a vacuum of less than about 0.2 mm of Hg.

-17-

5 The process of Claim 12 wherein the methylene chloride in step (d) is extracted with water to provide (II) in the water; the water with (II) is eluted through an ionic chromatographic column to provide aqueous fractions containing (II); the aqueous fractions are concentrated using a vacuum and heating to remove some of the water; a mixture of the concentrated aqueous fractions containing (II) is cooled to crystallize (II) from the concentrated solution and (II) is separated from the water.

-18-

The process of Claim 12 wherein the separated (II) in step (d) is dissolved in heated water and then the heated water is cooled to precipitate (II) which is separated from the water.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/04566

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC(5): C07H 17/00 U.S. Cl.: 536/27, 28, 29																				
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black; margin: 5px 0;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 25%; border: 1px solid black; padding: 5px;">Classification System</td> <td style="border: 1px solid black; padding: 5px;">Classification Symbols</td> </tr> <tr> <td style="border: 1px solid black; padding: 5px;">U.S. Cl.:</td> <td style="border: 1px solid black; padding: 5px;">536/24, 26, 27, 28, 29</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black; margin: 5px 0;">Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁸</div> <div style="text-align: center; padding: 10px 0;">APS</div>			Classification System	Classification Symbols	U.S. Cl.:	536/24, 26, 27, 28, 29														
Classification System	Classification Symbols																			
U.S. Cl.:	536/24, 26, 27, 28, 29																			
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; padding: 5px;">Category ⁹</th> <th style="width: 60%; padding: 5px;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 30%; padding: 5px;">Relevant to Claim No. ¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; padding: 5px;">Y</td> <td style="padding: 5px;">US, A, 3,413,282 (YOSHIKAWA ET AL) 26 November 1968, see entire document.</td> <td style="text-align: center; padding: 5px;">1-18</td> </tr> <tr> <td style="text-align: center; padding: 5px;">Y</td> <td style="padding: 5px;">US, A, 4,093,714 (TOLMAN ET AL) 06 June 1978, See col. 2, lines 58-69.</td> <td style="text-align: center; padding: 5px;">1-18</td> </tr> <tr> <td style="text-align: center; padding: 5px;">X</td> <td style="padding: 5px;">US, A, 4,123,609 (BEHNKE ET AL) 31 October 1978, see col. 1, line 51-col. 2, line 3.</td> <td style="text-align: center; padding: 5px;">1-18</td> </tr> <tr> <td style="text-align: center; padding: 5px;">A</td> <td style="padding: 5px;">US, A, 4,136,175 (RIDEOUT ET AL) 23 January 1979. See entire document.</td> <td style="text-align: center; padding: 5px;">1-18</td> </tr> <tr> <td style="text-align: center; padding: 5px;">Y</td> <td style="padding: 5px;">US, A, 4,357,324 (MONTGOMERY ET AL) 02 November 1982. See col. 4.</td> <td style="text-align: center; padding: 5px;">1-18</td> </tr> </tbody> </table>			Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	Y	US, A, 3,413,282 (YOSHIKAWA ET AL) 26 November 1968, see entire document.	1-18	Y	US, A, 4,093,714 (TOLMAN ET AL) 06 June 1978, See col. 2, lines 58-69.	1-18	X	US, A, 4,123,609 (BEHNKE ET AL) 31 October 1978, see col. 1, line 51-col. 2, line 3.	1-18	A	US, A, 4,136,175 (RIDEOUT ET AL) 23 January 1979. See entire document.	1-18	Y	US, A, 4,357,324 (MONTGOMERY ET AL) 02 November 1982. See col. 4.	1-18
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³																		
Y	US, A, 3,413,282 (YOSHIKAWA ET AL) 26 November 1968, see entire document.	1-18																		
Y	US, A, 4,093,714 (TOLMAN ET AL) 06 June 1978, See col. 2, lines 58-69.	1-18																		
X	US, A, 4,123,609 (BEHNKE ET AL) 31 October 1978, see col. 1, line 51-col. 2, line 3.	1-18																		
A	US, A, 4,136,175 (RIDEOUT ET AL) 23 January 1979. See entire document.	1-18																		
Y	US, A, 4,357,324 (MONTGOMERY ET AL) 02 November 1982. See col. 4.	1-18																		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"Δ" document member of the same patent family</p> </div> </div>																				
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border: 1px solid black; padding: 5px;"> Date of the Actual Completion of the International Search <div style="text-align: center; font-weight: bold;">06 September 1991</div> </td> <td style="width: 50%; border: 1px solid black; padding: 5px;"> Date of Mailing of this International Search Report <div style="text-align: center; font-weight: bold; font-size: 1.2em;">01 OCT 1991</div> </td> </tr> <tr> <td style="border: 1px solid black; padding: 5px;"> International Searching Authority <div style="text-align: center;">ISA/US</div> </td> <td style="border: 1px solid black; padding: 5px;"> Signature of Authorized Officer <div style="text-align: center;"> Anita Varma </div> </td> </tr> </table>			Date of the Actual Completion of the International Search <div style="text-align: center; font-weight: bold;">06 September 1991</div>	Date of Mailing of this International Search Report <div style="text-align: center; font-weight: bold; font-size: 1.2em;">01 OCT 1991</div>	International Searching Authority <div style="text-align: center;">ISA/US</div>	Signature of Authorized Officer <div style="text-align: center;"> Anita Varma </div>														
Date of the Actual Completion of the International Search <div style="text-align: center; font-weight: bold;">06 September 1991</div>	Date of Mailing of this International Search Report <div style="text-align: center; font-weight: bold; font-size: 1.2em;">01 OCT 1991</div>																			
International Searching Authority <div style="text-align: center;">ISA/US</div>	Signature of Authorized Officer <div style="text-align: center;"> Anita Varma </div>																			

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☒ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.